DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUL 25 2000

The Honorable John D. Dingell
Ranking Minority Member
Committee on Commerce
House of Representatives
Washington, D.C. 20515

Dear Mr. Dingell:

Thank you for your continued interest in the safety of prescription drugs available in the United States. This is in response to your letter of July 14, 2000, expressing your concern that two amendments recently adopted by the House of Representatives to the Agriculture Appropriations bill could seriously undermine the Prescription Drug Marketing Act (PDMA), and thus adversely affect public health. Specifically, you refer to amendments offered by Representatives Crowley and Coburn. You also referenced in your questions H.R. 3240, a bill passed by the House of Representatives, sponsored by Representative Gutknecht.

The Food and Drug Administration (FDA or the Agency) shares your concerns. We understand and are sympathetic to the Members' concerns about the high cost of prescription drugs, particularly for our nation's seniors. However, because of the significant impact these amendments will have on FDA's ability to protect the public health, they are not the appropriate solution to the drug pricing problem. The remedy to the drug-pricing problem should not be at the expense of safety.

You asked specific questions about the amendments. Your questions will be restated, followed by our response.

1. Please provide a detailed analysis on how (H.R. 4461 and H.R. 3240) would affect FDA's present operations regarding efforts to prevent misbranded or potentially dangerous drugs from entering the U.S. Specifically, please provide:

a. a description of how the present system now used by FDA works;
b. what the present system is intended to accomplish; and,
c. what changes would be required (and the potential effects of those changes) if this legislation passes in its present form.

Please include a discussion of how these amendments would affect the activities of other agencies, such as the U.S. Customs Service, with responsibilities for assuring the safety of imported prescription drugs.

Section 801 of the Federal Food, Drug and Cosmetic Act (FD&C Act or the Act) gives FDA the authority to refuse a product if it appears from the examination of samples or otherwise, to violate certain provisions of the FD&C Act, for example, if the product is adulterated, misbranded or unapproved. This enables our FDA investigators and U.S. Customs Service (Customs) officials to process entries efficiently. This was true back in 1906 when section 801 was first enacted and it is more salient today when products move freely around the world, facilitated by our expanded global market, the Internet, and trade agreements.

Under FDA's regulations, if a product appears as though it may be in violation of various statutory provisions it is subject to refusal of admission into the U.S. a Notice of Detention is sent to the importer, and the importer has the right to present evidence to FDA. Evidence may be submitted to FDA to demonstrate that the product they are offering for import: 1) does not appear to be violative, 2) is not a product that is subject to the Act, or, 3) may be reconditioned or relabeled and thus brought into compliance with the Act. Subsequent to refusal, section 801 gives the importer the opportunity to re-export the product.

Products entering the U.S. can be roughly grouped into three categories: commercial shipments, air couriers and mail deliveries, and personal baggage of individuals physically crossing the borders. Practically, the system works as follows:

Shipments of products imported for Commercial Distribution

When shipments of FDA-regulated products are imported for commercial distribution, the importer (or the importers' customhouse broker) submits entry and invoice data to FDA,

either electronically via Customs' ACS system, or via paper entry documents. FDA reviews the entry data for each shipment. Based on this "on screen" or paper review, FDA decides whether to allow the shipment to proceed without examination, to collect a sample for FDA lab analysis, or to detain the product pending a refusal decision based upon the appearance of a violation. If FDA lab analysis determines that the product complies with FDA requirements, the product is released; otherwise it is detained based on the results of the lab analysis. (FDA does limited testing for potency and identification. Under section 801(d)(1) it has not been necessary to test for authenticity as only the manufacturer may import into the United States.)

When a product is detained, a Notice of Detention is issued, and the importer is offered the opportunity to present evidence to FDA. If the evidence presented is sufficient to overcome the appearance of the violation, the product is released, and the importer may distribute it in domestic commerce. If the importer's evidence is not sufficient to overcome the appearance of a violation, the product is refused admission and must be exported or destroyed within 90 days.

Shipment of products for personal use imported via air express couriers

These shipments are processed similarly to commercial shipments except that FDA is notified of the entry by the air express courier rather than the importer. Based on the entry information supplied, FDA either allows the product to proceed without examination, or detains. Because of the normally lower value and larger number of such entries, it is relatively rare that FDA will physically sample and/or examine such entries. As is the case for commercial entries, FDA issues a Notice of Detention and gives the importer the opportunity to present evidence. If the importer presents sufficient evidence, admission and the product is released; otherwise it is refused must be exported or destroyed within 90 days.

Shipments of products for personal use imported via international mail

Mail shipments carried by the U.S. Postal Service are fundamentally different from commercial shipments or air express shipments. FDA does not receive any entry information

and depends upon Customs inspectors to identify mail entries of FDA-regulated products from and set them aside for FDA examination. Customs inspectors x-ray packages thought to contain FDA-regulated product, and if the x-ray indicates that the package does contain an FDA-regulated product the Customs Inspector opens the package and sets it aside for FDA examination. If an FDA Investigator determines that the article is in compliance with the applicable law and regulations it is sent on to the addressee. If the article appears to be subject to refusal, the addressee is sent a Notice of Detention, stating the reason why the article appears to be refusable, and informing the addressee of the right to contest FDA's decision. If the addressee fails to provide sufficient evidence or chooses not to reply the article is refused admission and either returned to the foreign sender (if it bears a valid return address) or it is destroyed.

"Warning Notices"

FDA has a history (dating back to at least the mid 1950s) of allowing humanitarian access to such products provided that such access does not pose an unreasonable risk to the public health. Initially, this practice was begun for foreign nationals on medication travelling in the U.S. or U.S. travelers who became ill while out of the country, so that they could bring in enough "urgent" supply to finish the course of the medication. It was expanded in the 1980s when no treatments were available in the U.S. for AIDS and some with possible promise were available in other countries. When an FDA Investigator exercises his or her enforcement discretion (under FDA's Personal Import Guidance) to release such a product to the importer, it may be "Released with Comment" stating that the product appears to fail to meet the relevant U.S. standard. In addition, a notice in the form of a letter may be attached to the shipment, alerting the importer that FDA cannot vouch for the safety or efficacy of the product. Although characterized as a "Warning Notice," this notice is in effect an attempt to provide the importer with information regarding the possible dangers posed by use of the product.

c. what changes would be required (and the potential effects of those changes) if this legislation passes in its present form.

H.R. 4461 (Amendments by Representatives Crowley and Coburn)

Both of the amendments prohibit FDA from expending funds to enforce section 801(d)(1). Under section 801(d)(1), no prescription or insulin-containing drugs manufactured in a state and exported may be reimported by anyone other than the manufacturer. Section 801(d)(1), in essence, codifies a presumption that U.S. manufactured drugs that are exported out of the U.S. and then imported back to the U.S., are adulterated, misbranded, or otherwise subject to refusal unless they are imported by the manufacturer. Under the Crowley amendment, anyone could reimport such drugs into the U.S., and FDA would have to take the added step of acquiring evidence that these drugs are adulterated, misbranded, or counterfeited. Removing the presumption of section 801(d)(1) would thus endanger the health and safety of Americans by placing an added evidentiary burden on an already overburdened FDA. Per the terms of the amendment, FDA would no longer be able to refuse the drugs as violative of 801(d)(1).

The Coburn amendment goes even further. It prohibits FDA from interfering with the importation of an approved product manufactured in Mexico, Canada, or the U.S. for any reason in any way. Thus if a routine inspection of a Mexican or Canadian firm producing an approved drug reveals good manufacturing practices (GMP), labeling, or other problems, FDA would be completely prohibited from interfering with the importation of that product. The Coburn prohibition extends not only to FDA's refusing the product at the border but also to FDA's taking of any other action that would interfere with its importation.

Thus, if an importer merely alleges that a product offered for import falls under the terms of the Coburn amendment, FDA would be prohibited from investigating the truth of importer's assertion or anything else about the product because, if the importer is correct, FDA's mere act of investigating the product would have interfered with importation of the product and would thus have violated the Coburn amendment. One could even argue that FDA could not even ask Customs to forward information about such products to FDA for review since merely expending effort in reviewing the information would interfere with the product's importation.

Once the product is imported, it is conceivable that FDA would be prohibited from pursuing a domestic enforcement action against the product under the Coburn amendment as well. Any domestic action could be construed as interfering with

subsequent importations of the same product and thus would be prohibited by the Coburn amendment. Even FDA's practice of sending informational letters to purchasers of drugs through the Internet could be construed as interfering with the product's importation and thus would be prohibited by the Coburn amendment. Finally, one could even make the argument that under the expansive language of the Coburn amendment, FDA could not withdraw approval of the product because that would interfere with the importation of a product that was approved at one time.

The expansive language of Coburn could also extend its application unintentionally to products from countries other than Mexico, Canada, and the U.S. Importers of drugs manufactured in other countries may have two possible means of gaining the pervasive protection of this amendment. First, as mentioned above, if an importer merely alleges that its product meets the terms of the Coburn amendment, FDA would be prohibited from investigating the truth of that assertion or taking any other action that would interfere with its importation lest the importer be found to have been right. Second, other parties to the General Agreement on Tariffs and Trade (GATT) may be able to argue that the preference given to Mexican and Canadian products outside the terms of a free trade agreement violates the GATT so that all other GATT members are entitled to similar treatment.

Seen in this light, the Coburn amendment could insulate any imported prescription drug from any FDA enforcement action no matter how dire a health or safety violation occurs. This would clearly have a devastating potential effect on consumer health and safety because FDA would be powerless to protect the public against any such threat that would arise.

Both of these amendments compromise the safety system designed to protect the American public from drugs that do not meet the standards of the FD&C Act.

H.R. 3240, "Drug Import Fairness Act of 2000"

As we understand it, the intent of this bill is to change the way in which the Agency issues warning notices for possibly violative products offered for import. We understand the intention is to provide the importer with more specific information about the nature of the possible violation.

However, as drafted, the bill extends far beyond this narrow objective. One key problem is that the term "warning notice" is defined so broadly in the bill that it arguably includes FDA's routine Notices of Detention. These notices are key legal documents that FDA must issue to importers when FDA believes drugs may "appear" violative in order to provide adequate notice to the importer of the FDA's pending decision. Therefore, they are designed to accommodate due process requirements prior to FDA taking final action on the product through refusal or admission. They inform the importers of what their options are and how they may wish to proceed to obtain release and avoid a refusal. By changing the criteria for these notices, the bill imposes an unnecessary burden on FDA with little benefit to the consumer.

More importantly, however, the bill would prevent FDA from refusing a product that appears to be restricted or prohibited in the country of origin or that appears to violate other Federal law such as medical device GMPs. FDA would have to prove the actual existence of a restriction, prohibition, or other violation before even sending the initial detention notice.

Nevertheless, in response to the interest in providing additional information to importers about the nature of the possible violation, the Agency is considering changes we might be able to make to our warning notices and notices of detention without unduly burdening the import screening process.

2. Please determine if either of these amendments would have any effect on FDA's ability to enforce good manufacturing practices (GMPs) in any foreign firms that ship drugs to the U.S. If so, please explain any potential effect on consumer health and safety.

As we read the amendments, they would have a devastating effect on FDA's ability to enforce GMPs in any foreign firms that ship drugs to the U.S. Currently, when FDA discovers GMP violations in foreign plants, it shares that information with FDA's District Offices thereby enabling them to refuse admission of any affected products shipped from that plant in the absence of any ameliorating evidence. This process is efficient, fair, and effective. As described above, the amendments would prohibit FDA from using this or any other means of interfering with the importation of drug products that do not comply with FDA's GMP requirements. Also this

would clearly have a devastating potential effect on consumer health and safety because FDA would be powerless to protect the public against any such threat that would arise.

3. Please provide a full description regarding what a "warning letter" is and how it is typically used by the FDA. Please compare this with correspondence that is sent by Customs.

Several different FDA written communications can fall under the description of "warning letters." We believe that the communication that is the subject of Representative Gutknecht's bill is a informational letter issued to individuals when granting imports under the Agency's personal importation policy.

The more usual FDA communication is a "Notice of FDA Action," that provides any importer (whether importing a product for personal or commercial purposes) the legal notice of FDA's pending admissibility decision, under section 801. This notice has two functions: to inform the importer of the reason why FDA believes the product may be refused admission, and to afford the opportunity for the importer to introduce evidence to the contrary. It describes the product and states the relevant violation (e.g., unapproved new drug, misbranded new drug, adulterated drug, etc.). Finally, it informs the importer of the right to introduce testimony to FDA regarding the admissibility of the product, as we have described above. A copy of this form is enclosed for your information.

For individuals crossing a border, as referenced above, the Agency provides the person with a second type of notice, which is called a "Dear Consumer" letter or "warning notice." This could more correctly be characterized as a "consumer information letter" rather than a "warning letter." The purpose of this letter is to advise the individual of the possible risks that may be associated with an unapproved product. When FDA exercises its enforcement discretion to permit individuals to import a 3-month supply of certain drugs for personal use, the "Dear Consumer" letter is our way of informing those individuals about the risks of importing such products. Specifically, the letter informs individuals that the imported drugs may be unapproved, adulterated or misbranded, and informs of the possible health consequences of taking such drugs. The letter also describes the law for importing unapproved products. A copy of this "Dear Consumer" letter also is enclosed.

4. **It appears that these amendments would directly affect the ability of FDA to send warning letters to consumers that purchase drugs over the Internet. As you know, some web sites appear to be covertly linked to foreign drug suppliers. When a consumer orders from such a site, it is not always obvious that they are dealing with an offshore supplier, and thus a potentially non-FDA approved facility. Often, warning letters may be the only indication that the Internet-ordered drugs originated from a foreign (and potentially dubious) source. Please indicate how this legislation could affect FDA's ability to protect consumers who purchased drugs in this way.**

As we read these amendments and the bill, the effect for drugs purchased over the Internet would be the same as all others. FDA's issuing these letters could be construed to constitute interference with imports covered by the Coburn amendment. Thus, FDA would be prohibited from expending funds to send these letters. Offshore importers who market to U.S. citizens could merely allege that these products meet the terms of the amendments and thus potentially completely insulate these shipments from FDA oversight. Opportunistic criminals may introduce counterfeit drugs into the U.S. by disguising them as approved U.S. pharmaceuticals. Unless such drugs could be proven counterfeit at the port of entry, which is a nearly impossible task, the Agency would be forced to admit them under this amendment, even if investigators could legitimately demonstrate that the drugs appeared to be counterfeit.

The Internet vastly amplifies the manner in which products may be purchased from foreign sources and shipped to the U.S.

5. **Please detail any other potential effects this legislation could have on FDA's ability to protect consumers from potentially dangerous drugs that originate abroad.**

These amendments will likely encourage the very sources of adulterated, misbranded, and unapproved drugs that were cut off by section 801(d)(1), to begin shipping again. FDA, with its limited resources, would be extremely hard-pressed to do the investigative work necessary to discover and stop these new sources of potentially harmful products.

6. **Finally, please provide technical assistance in the form of specific suggestions for legislative or regulatory changes that would be needed in order to facilitate the safe**

importation of prescription drugs by individuals, wholesalers, or retailers.

As you mentioned in your letter that "PDMA was designed to restore the integrity and control over the pharmaceutical market necessary to eliminate both the actual and potential health and safety problems before injury to the consumer could occur." You further state in your extension of remarks attached to your letter, "…legislation to modify the PDMA in a responsible fashion is an idea whose time has come."

We would be happy to provide technical assistance to you or your staff as you consider appropriate legislation.

In some of your questions, you asked that we provide information about the practices of or impact on the U.S. Customs Service. Rather than respond on Customs' behalf, I have taken the liberty of forwarding your letter to Customs' for reply.

Thank you for your interest in this matter. We look forward to working with you to continue to provide a system of safety that the American public has come to expect and deserve. If you have further questions, please let us know.

Sincerely,

Melinda K. Plaisier
Associate Commissioner
for Legislation

Enclosures

cc: The Honorable Thomas J. Bliley, Jr.
Chairman
Committee on Commerce
House of Representatives

U.S. Food & Drug Administration

Baltimore District Office

Notice of FDA Action

Entry Number: ---[redacted]
Reference No : [redacted]
Port of Entry: 5401, Washington D.C., DC

Notice Number: 1
June 26, 2000

[redacted]
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Shipper: unknown
unknown
unknown
Unknown Country [redacted]

A mail shipment addressed to you from a foreign country is being held by the post office at the request of the Food and Drug Administration (FDA).

Summary of Current Status of Individual Lines

No.	Product Description	Quantity	Current Status
001	GEROVITAL,GH3	100 Tablets	Detained 06-26-2000

The shipment may also contain other items not listed above.

DETAINED

The following products are subject to refusal of admission into the United States under authority of the Federal Food Drug and Cosmetic Act (FD&CA), Public Health Service Act (PHSA), or other related acts in that they appear to in violation as indicated below:

No.	Product Description		Respond By
001	GEROVITAL,GH3	100 Tablets	

July 17, 2000

FD&CA Section 505(a), 801(a)(3); UNAPPROVED NEW DRUG
The article appears to be a new drug without an approved new drug application.

All products of this kind must meet the requirements of the Federal Food Drug and Cosmetic Act or other laws enforced by the U.S. Food and Drug Administration. These laws are designed to protect you from, among other things, unsafe or misrepresented foods, drugs, biologics, cosmetics, devices, and other articles. These products do not appear to comply with the law.

Please direct your response to:
[redacted] Compliance Officer
U.S. Food & Drug Administration
[redacted]
[redacted]

(410) 962-3590 [redacted]
(410) 962-2219 (FAX)
[redacted]

This Notice does not in any manner accuse you of violating any law.

If you have a good reason to believe that the products comply with the law and wish to discuss it with us, you may come personally to this office or write to us. You must provide the entry number shown on the upper left of this notice whenever communicating with us.

Please direct your response to:
[redacted] Compliance Officer
U.S. Food & Drug Administration
~~2700 Broening Hwy~~ 900 Madison Ave.
Baltimore, MD ~~21222~~ 21201

(410) 962-3590 [redacted]
(410) 962-2219 (FAX)
[redacted]

If you do not wish to claim this shipment, you may disregard this notice and the shipment will be returned to sender without cost to you. The shipment will be returned automatically if we don't hear from you.

The shipment may contain items not included in this notice. If any portion of this shipment is refused admission, the U.S. Customs Service will cause the entire shipment to be returned to the sender or destroyed if the sender is unknown.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Minneapolis District
240 Hennepin Avenue
Minneapolis MN 55401-1999
Telephone: 612-334-4100

Dear Consumer:

This letter is to advise you that the Minneapolis District of the United States Food and Drug Administration (FDA) has examined a package addressed to you containing drugs which appear to be unapproved for use in the United States.

The United States Federal Food, Drug and Cosmetic Act (the Act) prohibits the interstate shipment (which includes importation) of unapproved new drugs. Thus, the importation of drugs that lack FDA approval, whether for personal use or otherwise, violates the Act. Unapproved new drugs are any drugs--including foreign-made versions of U.S. approved drugs--that have not been manufactured in accordance with and pursuant to an FDA approval. Under the Act, FDA may refuse admission to any drug that "appears" to be unapproved, placing the burden on the importer to prove that the drug sought to be imported is in fact approved by FDA. Absent evidence that the specific drugs sought to be imported from a foreign country have been manufactured pursuant to an approved new drug application, in the manufacturing facility permitted under the application, such drugs would appear to be unapproved new drugs subject to FDA enforcement action.

We appreciate that there is a significant cost differential between drugs available here and those in other countries. However, many drugs sold in foreign countries as "foreign versions" of approved prescription drugs sold in the United States are often of unknown quality with inadequate directions for use and may pose a risk to the patient's health. FDA approves a drug on the basis of scientific data proving it to be safe and effective. FDA approved labeling provides information on how and when the drug can be used to maximize effectiveness and minimize any harmful side effects. The manufacturing facilities and procedures for approved products are also carefully regulated by FDA to ensure product integrity. Since FDA cannot assure you the drug purchased in the foreign country would be the same product your physician's prescription is written for, we recommend the product covered by the prescription be acquired in the United States.

Because you are taking this medication under the care of a physician and we do not want to cause your medical treatment to be unduly affected, we are releasing this shipment. However, future shipments of these or similar drugs may be refused admission.

If you have any questions regarding this matter, please contact our office at (612) 334-4100 ext. 158.

Sincerely,

Lawrence R. Murphy
Compliance Officer
Minneapolis District

LRM/cd

Enclosure:
"Purchasing Medications Outside the United States"